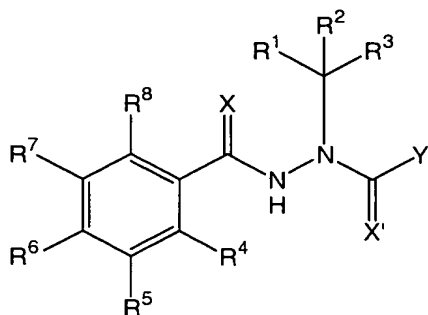


What is claimed is:

1. A compound of general formula:



wherein X and X' are independently O or S;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, n-propyl, isopropyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₄) alkenylalkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached; wherein R⁹ and R¹⁰ are independently: H, halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, benzoyloxy(C₁-C₃)alkyl, hydroxy(C₁-C₃)alkyl, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-

C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, (C₁-C₃)alkoxycarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkylcarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkanoyloxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl (-(CH₂)_nR^cR^e), oximo (-CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (-C=NOR^d), alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido (-C(O)NR^eR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (-C=NNHC(O)NR^eR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (-OC(O)NHR^g), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₃)trisubstituted-siloxy(C₁-C₃)alkyl (-(CH₂)_nSiOR^dR^eR^g); wherein n=1-3, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

- i when R⁹ and R¹⁰ are both H, or
- ii when either R⁹ or R¹⁰ are halo, (C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, or benzyloxy(C₁-C₃)alkyl, or
- iii when R⁵ and R⁶ do not together form a linkage of the type (-OCHR⁹CHR¹⁰O-),

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R¹ or R² is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R¹, R², and R³ is 10, 11, or 12.

2. The compound of claim 1, wherein:

X and X' are O;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl;

cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached; wherein R⁹ or R¹⁰ is H, and the alternate R⁹ or R¹⁰ is: H, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl $-(CH_2)_nR^cR^e$, oximo (-CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (-C=NO^d), alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido (-C(O)NR^fR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (-C=NNHC(O)NR^fR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (-OC(O)NHR^g), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₅)trisubstituted-siloxy(C₁-C₃)alkyl $-(CH_2)_nSiOR^dR^eR^g$; wherein n=1-3, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

- i when R⁹ and R¹⁰ are both H, or
- ii when R⁵ and R⁶ do not together form a linkage of the type (-OCHR⁹CHR¹⁰O-),

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R¹ or R² is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R¹, R², and R³ is 10, 11, or 12.

3. The compound of claim 2 wherein:

X and X' are O;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached; wherein R⁹ or R¹⁰ is H, and the alternate R⁹ or R¹⁰ is: H, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl (-CH₂)_nR^c, oximo (-CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (-C=NOR^d), alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido (-C(O)NR^eR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (-C=NNHC(O)NR^eR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (-OC(O)NHR^g), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxy, pentafluorophenyloxy(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₅)trisubstituted-siloxy(C₁-C₃)alkyl (-CH₂)_nSiOR^dR^eR^g); wherein n=1-3, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

- i when R⁹ and R¹⁰ are both H, or
- ii when R⁵ and R⁶ do not together form a linkage of the type (-OCHR⁹CHR¹⁰O-),

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1 , R^2 , and R^3 is 10, 11, or 12; and

when R^5 and R^6 together as a linkage of the type $(-OCHR^9CHR^{10}O-)$ form a ring with the phenyl carbons to which they are attached, and R^9 and R^{10} are not both H,

then R^1 and R^2 are (C_1-C_4) straight or branched alkyl, and R^3 is H or methyl.

4. The compound of claim 3 wherein:

X and X' are O;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (F, Cl, Br, I), (C_1-C_4) haloalkyl; or
- (b) substituted or unsubstituted 3-pyridyl, wherein the substituents are independently 1-4 H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (F, Cl, Br, I), (C_1-C_4) haloalkyl;

R^1 and R^2 are independently: H; cyano; cyano-substituted or unsubstituted (C_1-C_7) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C_2-C_7) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C_3-C_7) branched or straight-chain alkenylalkyl; or together the valences of R^1 and R^2 form a (C_1-C_7) cyano-substituted or unsubstituted alkylidene group ($R^aR^bC=$) wherein the sum of non-substituent carbons in R^a and R^b is 0-3;

R^3 is methyl;

R^4 , R^7 , and R^8 are independently selected from: H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (F, Cl, Br, I), (C_1-C_4) haloalkyl; and

R^5 and R^6 are independently: H, (C_1-C_4) alkyl, halo (F, Cl, Br, I), C_1-C_4 haloalkyl, (C_1-C_4) alkoxy, or together as a linkage of the type $(-OCHR^9CHR^{10}O-)$ form a ring with the phenyl carbons to which they are attached; wherein R^9 or R^{10} is H, and the alternate R^9 or R^{10} is: H, halo (C_1-C_2) alkyl, formyl, cyano (C_1-C_2) alkyl, carboxy, amino (C_1-C_2) alkyl, oximo $(-CH=NOH)$, (C_1-C_3) carboxamido $(-C(O)NR^eR^f)$, (C_1-C_2) semicarbazido $(-C=NNHC(O)NR^eR^f)$, aminocarbonyloxy $(-OC(O)NHR^8)$, pentafluorophenylloxycarbonyl, p-toluenesulfonyloxy (C_1-C_3) alkyl, methylthio (C_1-C_2) alkyl, methylsulfoxido (C_1-C_2) alkyl, methylsulfonyl (C_1-C_2) alkyl, or (C_1-C_5) trisubstituted-siloxy (C_1-C_3) alkyl $(-(CH_2)_nSiOR^dR^eR^f)$; wherein $n=1-3$, R^d represents a straight or branched hydrocarbon chain of the indicated length, R^e , R^f represent H or straight or branched hydrocarbon chains of the indicated length,

R^g represents (C_1-C_3) alkyl or aryl optionally substituted with halo or (C_1-C_3) alkyl, and R^c , R^d , R^e , R^f , and R^g are independent of one another;

provided that

- i) when R^9 and R^{10} are both H, or
- ii) when R^5 and R^6 do not together form a linkage of the type $(-OCHR^9CHR^{10}O-)$,

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1 , R^2 , and R^3 is 10, 11, or 12; and

when R^5 and R^6 together as a linkage of the type $(-OCHR^9CHR^{10}O-)$ form a ring with the phenyl carbons to which they are attached, and R^9 and R^{10} are not both H,

then R^1 and R^2 are methyl.

5. The compound of claim 4 selected from the group consisting of:

- a) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-hydroxymethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- b) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-[3-(tert-butyl-dimethyl-silanyloxymethyl)-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl]-hydrazide,
- c) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid,
- d) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid methyl ester,
- e) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-semicarbazidomethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- f) Phenyl-carbamic acid 7-[N'-tert-butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl ester,
- g) 3,5-Dimethyl-benzoic acid N'-[3-(2-amino-ethyl)-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl]-N-tert-butyl-hydrazide,

- h) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid pentafluorophenyl ester,
- i) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid methylamide,
- j) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-formyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- k) Toluene-4-sulfonic acid 7-[N'-tert-butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl ester,
- l) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-[3-(hydroxyimino-methyl)-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl]-hydrazide,
- m) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-cyanomethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- n) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(5-methyl-3-methylsulfanylmethyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- o) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-methanesulfonylmethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- p) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-fluoromethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- q) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-heptyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,
- r) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-heptyl)-N'-(4-ethyl-benzoyl)-hydrazide,
- s) 3,5-Dimethoxy-4-methyl-benzoic acid-N-(1-tert-butyl-heptyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,
- t) 3,5-Dimethoxy-4-methyl-benzoic acid-N-(1-tert-butyl-heptyl)-N'-(4-ethyl-benzoyl)-hydrazide,
- u) 2-Methoxy-nicotinic acid N-(1-tert-butyl-heptyl)-N'-(4-ethyl-benzoyl)-hydrazide,
- v) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-3,4,4-trimethyl-pent-2-enyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,

- w) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-2-cyano-vinyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,
- x) 3,5-Dimethyl-benzoic acid N-(1-butyl-2,2-dimethyl-pentyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide, and
- y) 3,5-Dimethyl-benzoic acid N-(1-butyl-2,2-dimethyl-pent-4-enyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide.

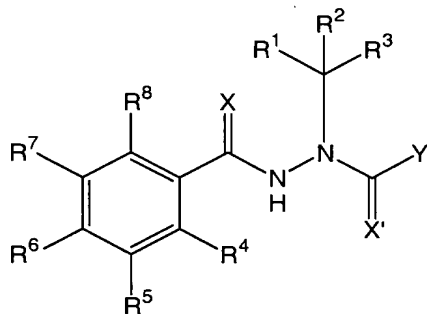
6. A method of modulating the expression of a target gene in a host cell, wherein the host cell includes a first gene expression cassette comprising a first polynucleotide encoding a first polypeptide comprising:

- (i) a transactivation domain;
- (ii) a DNA-binding domain; and
- (iii) a Group H nuclear receptor ligand binding domain;

a second gene expression cassette comprising:

- (i) a response element capable of binding to said DNA binding domain;
- (ii) a promoter that is activated by the transactivation domain; and
- (iii) said target gene;

the method comprising contacting said host cell with a compound of the formula:



wherein X and X' are independently O or S;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; or

- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, n-propyl, isopropyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₄) alkenylalkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached; wherein R⁹ and R¹⁰ are independently: H, halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, benzoyloxy(C₁-C₃)alkyl, hydroxy(C₁-C₃)alkyl, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, (C₁-C₃)alkoxycarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkylcarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkanoyloxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl (- (CH₂)_nR^cR^e), oximo (-CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (-C=NOR^d), alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido (-C(O)NR^eR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (-C=NNHC(O)NR^eR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (-OC(O)NHR^g), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₃)trisubstituted-siloxy(C₁-C₃)alkyl (- (CH₂)_nSiOR^dR^eR^g); wherein n=1-3, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

- i when R⁹ and R¹⁰ are both H, or
- ii when either R⁹ or R¹⁰ are halo, (C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, or benzoyloxy(C₁-C₃)alkyl, or

iii when R^5 and R^6 do not together form a linkage of the type $(-OCHR^9CHR^{10}O-)$, then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1 , R^2 , and R^3 is 10, 11, or 12.

7. The method of claim 6 wherein the compound is of the specified formula and:

X and X' are O;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro;

R^1 and R^2 are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R^1 and R^2 form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group ($R^aR^bC=$) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R^3 is H, methyl, ethyl, or cyano;

R^4 , R^7 , and R^8 are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, cyano, or nitro; and

R^5 and R^6 are independently: H, (C₁-C₄)alkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type $(-OCHR^9CHR^{10}O-)$ form a ring with the phenyl carbons to which they are attached; wherein R^9 or R^{10} is H, and the alternate R^9 or R^{10} is: H, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl $(-(CH_2)_nR^eR^f)$, oximo $(-CH=NOH)$, oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo $(-C=NOR^d)$, alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido $(-C(O)NR^eR^f)$, (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido $(-C=NNHC(O)NR^eR^f)$, semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy $(-OC(O)NHR^e)$, aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxy, pentafluorophenyloxy(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₃)trisubstituted-siloxy(C₁-C₃)alkyl $(-(CH_2)_nSiOR^dR^eR^f)$;

wherein $n=1-3$, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e , R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C_1-C_3) alkyl or aryl optionally substituted with halo or (C_1-C_3) alkyl, and R^c , R^d , R^e , R^f , and R^g are independent of one another;

provided that

- i when R^9 and R^{10} are both H, or
- ii when R^5 and R^6 do not together form a linkage of the type $(-OCHR^9CHR^{10}O-)$,

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1 , R^2 , and R^3 is 10, 11, or 12.

8. The method of Claim 7 wherein the compound is of the specified formula and:

X and X' are O;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (F, Cl, Br, I), (C_1-C_4) haloalkyl, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (F, Cl, Br, I), (C_1-C_4) haloalkyl, cyano, or nitro;

R^1 and R^2 are independently: H; cyano; cyano-substituted or unsubstituted (C_1-C_7) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C_2-C_7) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C_3-C_7) branched or straight-chain alkenylalkyl; or together the valences of R^1 and R^2 form a (C_1-C_7) cyano-substituted or unsubstituted alkylidene group ($R^aR^bC=$) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R^3 is H, methyl, ethyl, or cyano;

R^4 , R^7 , and R^8 are independently: H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (F, Cl, Br, I), (C_1-C_4) haloalkyl, cyano, or nitro; and

R^5 and R^6 are independently: H, (C₁-C₄)alkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type $(-OCHR^9CHR^{10}O-)$ form a ring with the phenyl carbons to which they are attached; wherein R^9 or R^{10} is H, and the alternate R^9 or R^{10} is: H, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl $(-(CH_2)_nR^eR^f)$, oximo $(-CH=NOH)$, oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo $(-C=NOR^d)$, alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido $(-C(O)NR^eR^f)$, (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido $(-C=NNHC(O)NR^eR^f)$, semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy $(-OC(O)NHR^g)$, aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₅)trisubstituted-siloxy(C₁-C₃)alkyl $(-(CH_2)_nSiOR^dR^eR^f)$; wherein $n=1-3$, R^e and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e , R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^e , R^d , R^e , R^f , and R^g are independent of one another;

provided that

- i when R^9 and R^{10} are both H, or
- ii when R^5 and R^6 do not together form a linkage of the type $(-OCHR^9CHR^{10}O-)$,

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1 , R^2 , and R^3 is 10, 11, or 12; and

when R^5 and R^6 together as a linkage of the type $(-OCHR^9CHR^{10}O-)$ form a ring with the phenyl carbons to which they are attached, and R^9 and R^{10} are not both H, then R^1 and R^2 are (C₁-C₄) straight or branched alkyl, and R^3 is H or methyl.

9. The method of Claim 8 wherein the compound is of the specified formula and:

X and X' are O;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl; or

(b) substituted or unsubstituted 3-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-3;

R³ is methyl;

R⁴, R⁷, and R⁸ are independently selected from: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, or together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached; wherein R⁹ or R¹⁰ is H, and the alternate R⁹ or R¹⁰ is: H, halo(C₁-C₂)alkyl, formyl, cyano(C₁-C₂)alkyl, carboxy, amino(C₁-C₂)alkyl, oximo (-CH=NOH), (C₁-C₃)carboxamido (-C(O)NR^eR^f), (C₁-C₂)semicarbazido (-C=NNHC(O)NR^eR^f), aminocarbonyloxy (-OC(O)NHR^g), pentafluorophenylloxycarbonyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, methylthio(C₁-C₂)alkyl, methylsulfoxido(C₁-C₂)alkyl, methylsulfonyl(C₁-C₂)alkyl, or (C₁-C₅)trisubstituted-siloxy(C₁-C₃)alkyl (- (CH₂)_nSiOR^dR^eR^f); wherein n=1-3, R^d represent a straight or branched hydrocarbon chain of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

- i) when R⁹ and R¹⁰ are both H, or
- ii) when R⁵ and R⁶ do not together form a linkage of the type (-OCHR⁹CHR¹⁰O-),

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R¹ or R² is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R¹, R², and R³ is 10, 11, or 12; and

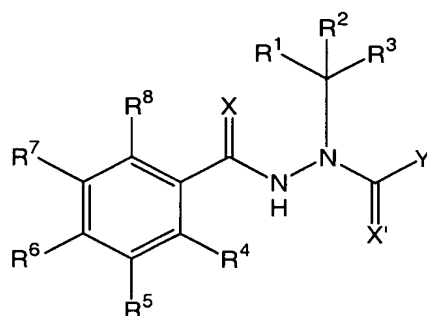
when R⁵ and R⁶ together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached, and R⁹ and R¹⁰ are not both H, then R¹ and R² are methyl.

10. The method of claim 9, wherein the compound is selected from the group consisting of:

- a) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-hydroxymethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- b) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-[3-(tert-butyl-dimethyl-silanyloxymethyl)-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl]-hydrazide,
- c) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid,
- d) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid methyl ester,
- e) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-semicarbazidomethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- f) Phenyl-carbamic acid 7-[N'-tert-butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl ester,
- g) 3,5-Dimethyl-benzoic acid N'-[3-(2-amino-ethyl)-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl]-N-tert-butyl-hydrazide,
- h) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid pentafluorophenyl ester,
- i) 7-[N'-tert-Butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxine-2-carboxylic acid methylamide,
- j) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-formyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- k) Toluene-4-sulfonic acid 7-[N'-tert-butyl-N'-(3,5-dimethyl-benzoyl)-hydrazinocarbonyl]-8-methyl-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl ester,
- l) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-[3-(hydroxyimino-methyl)-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl]-hydrazide,
- m) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-cyanomethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,

- n) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(5-methyl-3-methylsulfanylmethyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- o) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-methanesulfonylmethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- p) 3,5-Dimethyl-benzoic acid N-tert-butyl-N'-(3-fluoromethyl-5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide,
- q) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-heptyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,
- r) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-heptyl)-N'-(4-ethyl-benzoyl)-hydrazide,
- s) 3,5-Dimethoxy-4-methyl-benzoic acid-N-(1-tert-butyl-heptyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,
- t) 3,5-Dimethoxy-4-methyl-benzoic acid-N-(1-tert-butyl-heptyl)-N'-(4-ethyl-benzoyl)-hydrazide,
- u) 2-Methoxy-nicotinic acid N-(1-tert-butyl-heptyl)-N'-(4-ethyl-benzoyl)-hydrazide,
- v) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-3,4,4-trimethyl-pent-2-enyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,
- w) 3,5-Dimethyl-benzoic acid N-(1-tert-butyl-2-cyano-vinyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide,
- x) 3,5-Dimethyl-benzoic acid N-(1-butyl-2,2-dimethyl-pentyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide, and
- z) 3,5-Dimethyl-benzoic acid N-(1-butyl-2,2-dimethyl-pent-4-enyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide.

11. A method to modulate the expression of one or more exogenous genes in a subject, comprising administering to the subject an effective amount of a ligand of the formula:



wherein X and X' are independently O or S;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, n-propyl, isopropyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₄) alkenylalkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached; wherein R⁹ and R¹⁰ are independently: H, halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, benzyloxy(C₁-C₃)alkyl, hydroxy(C₁-C₃)alkyl, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, (C₁-C₃)alkoxycarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkylcarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkanoyloxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl (- (CH₂)_nR^cR^d), oximo (-CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (-C=NOR^d), alkoximo(C₁-

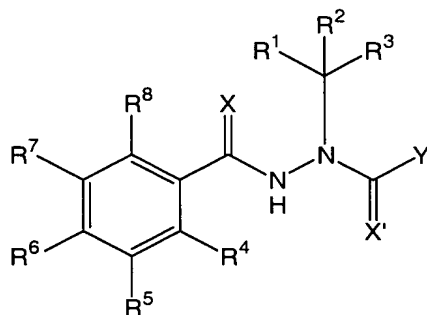
C₃)alkyl, (C₁-C₃)carboxamido (-C(O)NR^eR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (-C=NNHC(O)NR^eR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (-OC(O)NHR^g), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₃)trisubstituted-siloxy(C₁-C₃)alkyl $-(\text{CH}_2)_n\text{SiOR}^d\text{R}^e\text{R}^g$; wherein $n=1-3$, R^e and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

- i when R⁹ and R¹⁰ are both H, or
- ii when either R⁹ or R¹⁰ are halo, (C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, or benzoyloxy(C₁-C₃)alkyl, or
- iii when R⁵ and R⁶ do not together form a linkage of the type $(-\text{OCHR}^9\text{CHR}^{10}\text{O}-)$,

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R¹ or R² is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R¹, R², and R³ is 10, 11, or 12.

12. A method for regulating endogenous or heterologous gene expression in a transgenic subject comprising contacting a ligand with an ecdysone receptor complex within the cells of the subject, wherein the cells further contain a DNA binding sequence for the ecdysone receptor complex when in combination with the ligand and wherein formation of an ecdysone receptor complex-ligand-DNA binding sequence complex induces expression of the gene, and where the ligand has the following formula:



wherein X and X' are independently O or S;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently from 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, n-propyl, isopropyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₄) alkenylalkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (–OCHR⁹CHR¹⁰O–) form a ring with the phenyl carbons to which they are attached; wherein R⁹ and R¹⁰ are independently: H, halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, benzoyloxy(C₁-C₃)alkyl, hydroxy(C₁-C₃)alkyl, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, (C₁-C₃)alkoxycarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkylcarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkanoyloxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl (–(CH₂)_nR^cR^e), oximo (–CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (–C=NOR^d), alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido (–C(O)NR^eR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (–C=NNHC(O)NR^eR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (–OC(O)NHR^e), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₃)trisubstituted-siloxy(C₁-C₃)alkyl (–(CH₂)_nSiOR^dR^eR^f); wherein n=1-3, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon

chains of the indicated length, R^g represents (C_1-C_3) alkyl or aryl optionally substituted with halo or (C_1-C_3) alkyl, and R^c , R^d , R^e , R^f , and R^g are independent of one another;

provided that

- i when R^9 and R^{10} are both H, or
- ii when either R^9 or R^{10} are halo, (C_1-C_3) alkyl, (C_1-C_3) alkoxy (C_1-C_3) alkyl, or benzyloxy (C_1-C_3) alkyl, or
- iii when R^5 and R^6 do not together form a linkage of the type $(-OCHR^9CHR^{10}O-)$,

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1 , R^2 , and R^3 is 10, 11, or 12.

13. The method of Claim 12, wherein the ecdysone receptor complex is a chimeric ecdysone receptor complex and the DNA construct further comprises a promoter.

14. The method of Claim 12, wherein the subject is a plant.

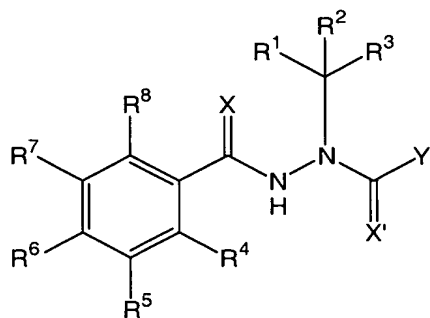
15. The method of Claim 12, wherein the subject is a mammal.

16. A method of modulating the expression of a gene in a host cell comprising the steps of:

- a) introducing into the host cell a gene expression modulation system comprising:
 - i) a first gene expression cassette that is capable of being expressed in a host cell comprising a polynucleotide sequence that encodes a first hybrid polypeptide comprising:
 - (a) a DNA-binding domain that recognizes a response element associated with a gene whose expression is to be modulated; and
 - (b) an ecdysone receptor ligand binding domain;
 - ii) a second gene expression cassette that is capable of being expressed in the host cell comprising a polynucleotide sequence that encodes a second hybrid polypeptide comprising:
 - (a) a transactivation domain; and
 - (b) a chimeric retinoid X receptor ligand binding domain; and
 - iii) a third gene expression cassette that is capable of being expressed in a host cell comprising a polynucleotide sequence comprising:

- (a) a response element recognized by the DNA-binding domain of the first hybrid polypeptide;
- (b) a promoter that is activated by the transactivation domain of the second hybrid polypeptide; and
- (c) a gene whose expression is to be modulated; and

b) introducing into the host cell a ligand of the formula:



wherein X and X' are independently O or S;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, n-propyl, isopropyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; and

R^5 and R^6 are independently: H, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₄) alkenylalkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (–OCHR⁹CHR¹⁰O–) form a ring with the phenyl carbons to which they are attached; wherein R^9 and R^{10} are independently: H, halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, benzoyloxy(C₁-C₃)alkyl, hydroxy(C₁-C₃)alkyl, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, (C₁-C₃)alkoxycarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkylcarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkanoyloxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl (–(CH₂)_nR^cR^e), oximo (–CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (–C=NOR^d), alkoximo(C₁-C₃)alkyl, (C₁-C₃)carboxamido (–C(O)NR^eR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (–C=NNHC(O)NR^eR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (–OC(O)NHR^g), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₅)trisubstituted-siloxy(C₁-C₃)alkyl (–(CH₂)_nSiOR^dR^eR^g); wherein n=1-3, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

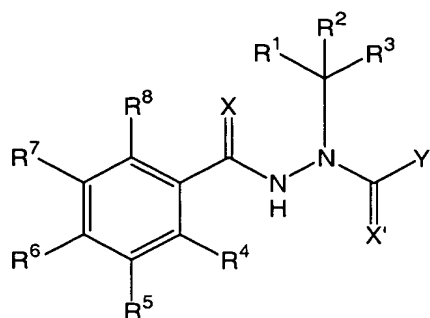
provided that

- i when R^9 and R^{10} are both H, or
- ii when either R^9 or R^{10} are halo, (C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, or benzoyloxy(C₁-C₃)alkyl, or
- iii when R^5 and R^6 do not together form a linkage of the type (–OCHR⁹CHR¹⁰O–),

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1 , R^2 , and R^3 is 10, 11, or 12.

17. A method for producing a polypeptide comprising the steps of:

- a) selecting a cell which is substantially insensitive to exposure to a ligand comprising the formula:



wherein X and X' are independently O or S;

Y is:

- (a) substituted or unsubstituted phenyl wherein the substituents are independently 1-5 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; or
- (b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substituents are independently 1-4 H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro;

R¹ and R² are independently: H; cyano; cyano-substituted or unsubstituted (C₁-C₇) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C₂-C₇) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C₃-C₇) branched or straight-chain alkenylalkyl; or together the valences of R¹ and R² form a (C₁-C₇) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R³ is H, methyl, ethyl, n-propyl, isopropyl, or cyano;

R⁴, R⁷, and R⁸ are independently: H, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₂-C₄)alkenyl, halo (F, Cl, Br, I), (C₁-C₄)haloalkyl, hydroxy, amino, cyano, or nitro; and

R⁵ and R⁶ are independently: H, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₄) alkenylalkyl, halo (F, Cl, Br, I), C₁-C₄ haloalkyl, (C₁-C₄)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (-OCHR⁹CHR¹⁰O-) form a ring with the phenyl carbons to which they are attached; wherein R⁹ and R¹⁰ are independently: H, halo, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, benzoyloxy(C₁-C₃)alkyl, hydroxy(C₁-C₃)alkyl, halo(C₁-C₃)alkyl, formyl, formyl(C₁-C₃)alkyl, cyano, cyano(C₁-C₃)alkyl, carboxy, carboxy(C₁-C₃)alkyl, (C₁-C₃)alkoxycarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkylcarbonyl(C₁-C₃)alkyl, (C₁-C₃)alkanoyloxy(C₁-C₃)alkyl, amino(C₁-C₃)alkyl, (C₁-C₃)alkylamino(C₁-C₃)alkyl (- (CH₂)_nR^c), oximo (-CH=NOH), oximo(C₁-C₃)alkyl, (C₁-C₃)alkoximo (-C=NO^d), alkoximo(C₁-

C₃)alkyl, (C₁-C₃)carboxamido (-C(O)NR^eR^f), (C₁-C₃)carboxamido(C₁-C₃)alkyl, (C₁-C₃)semicarbazido (-C=NNHC(O)NR^eR^f), semicarbazido(C₁-C₃)alkyl, aminocarbonyloxy (-OC(O)NHR^g), aminocarbonyloxy(C₁-C₃)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C₁-C₃)alkyl, p-toluenesulfonyloxy(C₁-C₃)alkyl, arylsulfonyloxy(C₁-C₃)alkyl, (C₁-C₃)thio(C₁-C₃)alkyl, (C₁-C₃)alkylsulfoxido(C₁-C₃)alkyl, (C₁-C₃)alkylsulfonyl(C₁-C₃)alkyl, or (C₁-C₅)trisubstituted-siloxy(C₁-C₃)alkyl (-CH₂)_nSiOR^dR^eR^g); wherein n=1-3, R^e and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C₁-C₃)alkyl or aryl optionally substituted with halo or (C₁-C₃)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

- i when R⁹ and R¹⁰ are both H, or
- ii when either R⁹ or R¹⁰ are halo, (C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, or benzyloxy(C₁-C₃)alkyl, or
- iii when R⁵ and R⁶ do not together form a linkage of the type (-OCHR⁹CHR¹⁰O-),

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R¹ or R² is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R¹, R², and R³ is 10, 11, or 12;

b) introducing into the cell:

1) a DNA construct comprising:

- i) an exogenous gene encoding the polypeptide; and
- ii) a response element;

wherein the gene is under the control of the response element; and

2) an ecdysone receptor complex comprising:

- i) a DNA binding domain;
- ii) a binding domain for the ligand; and
- iii) a transactivation domain; and

c) exposing the cell to the ligand.